REMARKS

Claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 were pending in the application. New claim 114 has been added. Accordingly, after the amendments presented herein have been entered, claims will be pending.

Support for the new claim can be found throughout the specification and claims as filed. Specifically, support for new claim 114, can be found at, for example, page 10 lines 14-15, page 30 lines 13-14, and Examples 4 and 5.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 103(a)

The Examiner has maintained the rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 USC 103(a) as being unpatentable over 5,859,312 ("Littman et al.") in view of Monbarts et al., McMurry et al., Rowen et al. and Rack et al.

Applicants traverse this rejection for the following reasons.

The Examiner maintains that the claimed invention is unpatentable over Littman et al. in view of Mombaert et al., McMurry et al, Rowen et al. and Rack et al. However, the cited references alone or in combination fail provide the requisite teachings of a non-human transgenic animal capable of producing heterologous T-cell receptors comprising unrearranged human T-cell receptor alpha and beta loci wherein said animal is capable of productive rearrangement of said human T-cell receptor α and β loci to encode functional heterologous T-cell receptors.

The Examiner believes that Littman et al. teach general methods for producing transgenic non-human animals which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction proteins as a results of inactivation of the endogenous lymphocyte transduction protein gene loci. The Examiner further believes that Littman et al. teach methods of generating such transgenic animals in which the lymphocyte transduction proteins are TCR α and β gene products. The Examiner indicated that Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which

the TCR loci are inactivated and human unrearranged TCR V, D, and/or J, and C genes have been inserted into the genome. The Examiner supplements the teachings of Littman et al. with the teachings of Mombaerts et al. and McMurry et al. The Examiner states that McMurry et al. supplements Littman et al. by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus and that these mice are capable of rearranging the human TCR delta gene locus. However, as indicated in previous responses and acknowledged by the Examiner, McMurry et al. used a TCR delta gene minilocus that mutated to prevent rearranged transcripts from encoding functional TCR protein. Thus, McMurry et al. does not teach transgenic mice comprising unrearranged TCR loci that productively rearrange to encode functional TCR molecules or transgenic mice where the expression of functional transgenic TCR molecules is necessary for T-cell development, T-cell maturation or antigen stimulated responses. Littman et al. also does not teach such transgenic mice. In contrast, the instant invention provides for transgenic animals carrying unrearranged human T-cell receptor alpha and beta loci, which are ***capable of productive rearrangements to encode a functional heterologous T-cell receptor***. The instant invention also provides for such transgenic animals that express heterologous T-cell receptor necessary to effect T-cell development, produce mature, functional T-cells, or elicit an effective antigen-stimulated response.

The Examiner believes that the teachings of McMurry et al. regarding similarities between the Ig and TCR loci and the state of the art of transgenic mice comprising unrearranged Ig loci would have led the skilled artisan to have a reasonable expectation of success that the presence of unrearranged TCR loci in transgenic mice would lead to productive rearrangement and expression of functional TCR in T cells. While McMurry et al. describe some similarities between Ig and TCR loci, they also indicate that there are multiple levels of cell type-specific and temporal regulatory controls that distinguish the productive rearrangement and functional expression of Ig and TCR molecules (see page 4553 2nd column). In addition, there are well known difference in the nature of allelic exclusion between the IgG heavy and light chain genes and the TCR β and α chain genes (see abstract of Sleckman et al. 1998. J. Exp. Med. 188: 1465-1471 submitted herewith). Most significantly, generation of mature T-cells with α/β TCRs requires productive TCR loci rearrangement, TCR gene expression and progression through the T-cell development pathway controlled by proper formation of functional pre-TCR molecules composed of the TCR β and pT α proteins, subsequent formation of functional α/β TCR

molecules and the positive/negative selection processes in the thymus. Both the pre-TCR and αβ TCR must also interact with various other endogenous proteins (i.e. CD3γ, CD3ζ, CD3δ, CD3ε) to mediate proper signaling controlling T-cell development and responses. For example, productive rearrangement of the TCR β chain locus and expression of the TCR β chain during the $CD44^{-}CD25^{+}$DN stage of thymocyte development permits formation of the pre-TCR with the pT α chain. This event represents perhaps the most critical cell-fate determining event in αβ T-cell development. Formation of the functional pre-TCR provides survival and proliferative signals in the transition from the DN to DP stage, terminates further TCR β gene rearrangement through allelic exclusion, and controls subsequent differentiation (i.e. TCR α chain expression and rearrangement) in the DP stage (see page 640 2nd column, Kruisbeek et al. 2000. Immunol. Today 21: 637-644 submitted herewith). In addition the signaling pathways mediated by the pre-TCR are different for each of these activities (see Figure 3, Kruisbeek et al.). The development of antibody responses in transgenic mice carrying unrearranged Ig loci do not rely on the formation or signaling of functional pre-TCR or TCRs comprising transgene-encoded products. Moreover there is nothing in the transgenic IgG mouse literature to teach or suggest that mice carrying an unrearranged human TCR β locus could generate a human TCR β chain capable of forming a functional complex with the endogenous pT α chain necessary to permit proper T-cell development, T-cell maturation or antigen-stimulated T-cell responses. In contrast to the teaching of Littman et al and McMurry et al., Applicants have shown that it is possible to generate mature T-cells carrying productively rearranged human TCR genes and expressing functional human TCRs in transgenic mice carrying unrearranged human T-cell receptor loci.

Claim 114 has been amended to provide for non-human transgenic animals, wherein the transgenic human TCR α locus contains all of the human TCR α V, J and C genes. New claim 115 has been added to provide for such non-human transgenic animals, wherein transgenic human TCR α locus also contains all of the human TCR β V, D, J and C genes. None of the cited references teach or suggest transgenic animals that contain human TCR α locus with all of the human TCR α V, J and C genes. Rack et al. is relied on by the Examiner to disclose the human TCR α loci sequence. However, Rack only teaches a construct containing a portion of the TCR α/δ loci genes (see Rack et al. at pages 1233-1234).

New claim 116 has been added to provide for non-human transgenic animals, wherein the animals are capable of producing a repertoire of heterologous TCRs. None of the cited references teach or suggest such transgenic animals.

Finally, new claims 117 and 118 have been added to provide for non-human transgenic animals, expression of the heterologous T-cell receptors is necessary for T-cell development, T-cell maturation or antigen stimulated responses and that expression of the heterologous T-cell receptors on pre-T cells affects these processes. As indicated above, none of the cited references teach or suggest such transgenic animals.

Accordingly, the claims as pending are not obvious in view of the cited references. Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claim 114 Under 35 USC 112, First Paragraph

The Examiner has rejected claim 114 under 35 USC 112, first paragraph as being indefinite. While in no way acquiescing to the validity of the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended claim 114 as to better define the claimed subject matter.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the forgoing rejection.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____

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